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PETHIDINE RASH: ITS INFLUENCE ON PEROPERATORY HEMORRHAGE (RASH --ETC(U)  
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PETHIDINE RASH: ITS INFLUENCE ON PEROPERATORY HEMORRHAGE (\*)

by R. Schnoebelen, D. Cakmur, J. Coblenz, J. Muller, and E. Forster (\*\*)  
(Colmar)

(\*) Communication presented to the Provincial Session of the French Society of Anesthesia, Analgesia, and Resuscitation on 7 November 1964.

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It has always been known that, in people who are being operated on, the extent or importance of the hemorrhage varies greatly from one subject to the next and what Baumann wrote is still true: "It is absolutely impossible to predict in a standard operation what the blood loss will be for a given patient." The blood loss figures, recently registered by Merle d'Aubigne and also Aboulker reveal the entire imprecision connected with peroperative hemorrhage. With respect to arthroplasty of the hip, depending upon the particular case, Merle d'Aubigne noted blood losses between 112 and 1,536 ml while, for prostatectomies, Aboulker reported figures between 100 and 1,000 ml. There was no valid explanation for these variations.

The problem of peroperative bleeding has preoccupied us since 1957 and over these past 8 years we have tried to find an explanation for it in the course of something like 26,000 anesthetics which we performed. It is not our purpose here to take up again the question of peroperative hemorrhage in detail but rather to study certain particular aspects. Thus we will right away eliminate hemorrhages caused by the activities of the surgeon himself (section of a vessel); they are purely technical and go beyond the framework which we have set up for ourselves here; likewise not within this framework are diffuse hemorrhages which reveal preexisting hemostasis trouble or trouble developing in the course of intervention (hemophilia, thrombopenia, and fibrinolysis).

We can group the causes of diffuse hemorrhages under three headings: plasmatic, plate-like, and vascular. We intend to tackle here only the problem of bleeding of vascular origin.

The first factor in bleeding of vascular origin, arterial tension [pressure], is well known; the other one--the interplay of peripheral vascular vasomotors--is less well known and there is still much imprecision around it.



It is certain that arterial tension plays an important role in bleeding and it is no less certain that the tension figure is only a secondary phenomenon in a patient who is otherwise normal in peripheral vascular respects. One can as a matter of fact observe minor bleeding in a patient with serious hypertension or, conversely, major bleeding in a person with hypotension. To have a patient bleed, it is never less indispensable that his arterial system be under a certain tension and that his vessels be supplied with blood. This notion has given rise to the method of controlled hypotension which, in the course of reputedly hemorrhagic interventions, is designed artificially to lower the arterial tension and thus to diminish the bleeding. But this technique, as we know, does not work in about 20% of the cases and the result we get is not regularly proportional to the drop in the tension which we bring about. Although it has been thoroughly studied, controlled hypotension still leaves enough unexplained points one of the most important of which is the persistence of abundant and diffuse bleeding in spite of a very definite tension drop. To understand this phenomenon, it is indispensable to bring in the second vascular factor, the factor of the vasomotricity of the small vessels.

The vasomotricity of the small vessels is well known to the surgeon and he is on the alert for it. He hopes to find small peripheral vessels contracting rapidly and thus to drain [exhaust] the diffuse hemorrhage in a few minutes. This is why it seemed rather curious that the state of vasomotricity of the small vessels has aroused so little attention among all those who worked on peroperative hemorrhages. Any anesthetist knows of course that, when there is hypercapnia, the operative field bleeds because at that moment there is a massive vasodilatation of the arterioles and the capillaries. We, for our part, think that the state of peripheral vasomotricity and the tone of the arteriole-capillaries represent one of the essential causes which present us either with a dry or a wet operative field. We will now try to prove this on the basis of observations which we were able to make in our anesthetics.

Over these past several years we have been able to evidence a correlation between abnormal bleeding and a venous reaction which came in response to an injection of pethidine during anesthetic induction. We noted that, even when the venous reaction was feeble, there could be a definite increase in the bleeding and that there was no interdependence between the intensity of bleeding and the intensity of the venous phenomenon. We believe that the reaction, which we observed, may be one element among all of the factors in abnormal bleeding that cannot be neglected; pethidine is a drug currently used in anesthesia; it is also known, as we shall see, by virtue of the fact that it brings about a reaction due to the release of histamine.

To determine the specific facts involved, we studied peroperative bleeding in two groups of persons who were operated on and to simplify the data involved in the problem, we decided to reduce them to a simple constant; we therefore confined ourselves to the thorax opening time, a

surgical sequence which remains practically identical, regardless of the surgeon performing it.

We grouped our observations in two sets:

The one included 107 cases all of which presented a venous reaction to pethidine injection. In this group we observed abnormally voluminous bleeding 100 times and ordinary bleeding 7 times.

The second set included 128 patients who revealed neither a venous reaction to pethidine injection nor abnormal bleeding. In their cases, hemostasis was easy and of the kind usually encountered. This is the control group.

The bleeding was estimated [measured] each time by the surgeon and the anesthetist. The visual observation was completed by weighing the compresses which, although imprecise, was the only method we had available. Here are the data we recorded: an average blood loss of 86.14 ml for patients being operated on (without venous reaction to pethidine) and an average loss of 118.83 ml for those who presented a venous reaction and seemed to us to have bled in an abnormally voluminous fashion. There is an increase of only about 40% between these two figures. This rate does not correspond to the visual estimation which is much more alarming and which we made here; the two series of patients were differentiated more by their tendency toward diffuse bleeding rather than by the quantity of blood actually lost. As far as the hemorrhage itself is concerned, it is manifested above all on the level of the skin and the subcutaneous tissues and almost always on the level of the muscle layers. What we saw seemed to us, at any point, to be similar to what one can observe in hemostasis disorders: diffuse and sustained hemorrhage which is an irritation to the surgeon because he can bring it under control only through compression using hot serum. The surgeon moreover often asked us, before the bleeding, to check the coagulation time in order to eliminate possible trouble arising from blood crasis. To all of these data we might also add the seven persons operated on in the first set with venous reaction who did not bleed abnormally but who, on the other hand, revealed a drop in the arterial tension [pressure] amounting to between three and six points.

The venous reaction following pethidine injection, which we observed, consists of three phenomena:

A redness which appears at the point of venous puncture several minutes after the pethidine injection, a redness which quickly spreads over the entire path of the vein, which reaches its tributaries and in certain cases even faithfully reproduces the layout of the veins of the upper member and the hemithorax. We think that it is not impossible that these reactions spread to the veins of the deep tissues and even to the big venous trunk although we have no proof of that.



The second component is an arteriolar dilatation which widely encroaches upon the surrounding skin regions. This is an axon reflex.

Edematous infiltration, which appears on the venous path, constitutes the third component; it reveals a change in capillary permeability.

Hemorrhage is Function of Arterial Tension and Contracting Power of Cut Vessel

T.A.	① PRESSION ARTERIELLE DANS LE VAISSEAU	② ETAT DU VAISSEAU	③ IMPORTANCE DE L'HEMORRAGIE
Normale	Normale	④ POUVOIR DE VASO - CONSTRUCTION VASCULAIRE PERIPHERIQUE CONSERVE	⑤ HEMORRAGIE PEU IMPORTANTE OU NULLE
Conservée	Normale	⑥ POUVOIR DE VASO - CONSTRUCTION VASCULAIRE PERIPHERIQUE ANNULE	⑦ HEMORRAGIE ANORMALE OU IMPORTANTE
Abaissee	abaissee	⑧ POUVOIR DE VASO - CONSTRUCTION VASCULAIRE PERIPHERIQUE ANNULE	⑧ HEMORRAGIE FAIBLE OU NULLE

Legend: 1--arterial pressure in vessel; 2--condition of vessel; 3--extent of hemorrhage; 4--peripheral vascular vasoconstriction power retained; 5--minor hemorrhage or none at all; 6--peripheral vascular vasoconstriction power lost; 7--abnormal or voluminous hemorrhage; 8--feeble or no hemorrhage; 9--retained; 10--lowered; T.A.--arterial tension.

We are thus dealing here with a "triple reaction." This reaction to pethidine--described by Zuck (14) and then by Pearce (9)--is at any point similar to the one evidenced by Finer and Partington which the injection of histamine brings about on the level of the skin. Thus we thought that the "triple reaction," which appears after the i.v. injection of pethidine, is due to the release of histamine from the tissues in contact with this drug. We know that histamine acts on the smooth muscle fibers of the vessels (3, 8, 12, 13). It paralyzes these fibers and by virtue of that fact brings about a passive vasodilatation of the arterioles and the capillaries. In man, the phenomenon is localized essentially on the level of the skin,

the subcutaneous cellular tissue, and the muscles. We also know that histamine, abnormally released by the cells, is involved in the regulation of the local vascular tone and that it governs the blood flow rate in the tissues. We also know that a massive release of histamine brings about an intense arterial-capillary dilatation and produces an appreciable drop in the arterial tension (1, 3, 4, 12, 13). It is furthermore through a release of histamine that Finer and Partington explain the tension drops which one can observe after i.v. injection of pethidine.

For our part, we think that one can explain many of the cases of voluminous bleeding which one observes in the light of histamine. In cases where we found a histaminic reaction to pethidine, we as a matter of fact encountered all of the elements which explain these facts. We will now analyze them in detail.

First of all, let us take vasomotricity. The vascular tonus and the vasoconstriction of the arterioles and the capillaries are essential things in hemostasis and Laborit recently drew attention to them (15). When the surgeon cuts a tissue where there is an intense arteriolar and capillary dilatation, the bleeding is more voluminous if the vessels are tonic and capable of vasoconstriction, which is normally the case. The hemorrhage becomes troublesome and irritating when practically all of the small vessels are unable to contract. They then behave like venules and they remain wide open and dribble blood. Their lumen is closed only by the pressure exerted by the surrounding tissues. We observed this in our patients. Let us add that the loss of vasomotricity has another consequence: it has an effect on the initial time of normal hemostasis which is assured by a vasomotor phenomenon. It is regrettable that one cannot materialize this phenomenon but, if one does not have any recording apparatus that enables us to do so (2), the fact does nevertheless exist. It may also be that the loss of vasomotricity on the part of the arterioles and capillaries has repercussions on the second factor in bleeding, that is, arterial tension, which we will now study in terms of its interreaction on vasomotricity and on the persistence of bleeding.

Arterial tension (which, in case of vasomotricity loss, can point to a considerable drop (1, 3, 4, 10, 12, 13)) plays a capital role in the intensity of bleeding depending upon whether it is combined with vasomotor disorders [and] it is [then] either high or low.

If arterial tension is high, the hemorrhage may assume large proportions. Under pressure, the blood then encounters no resistance in the small atonic vessels which have lost all or almost all of their contractility. There is no mechanism to oppose the extravasation of blood from these vessels which remain supplied with blood. These conditions were encountered in our patients as a result of histamine reaction. The bleeding was heavy and the tension figure remained normal.



But if the arterial pressure drops at the same time that the vessels lose their tonus, it may be that the hemorrhage will not be more intensive than it usually is because the arterial pressure, which exists in the small vessels, does not manage to force either spontaneous collapsus [collapse] or the residual arterial tonus, even if the latter is only very feeble. Thus we explain what we observed in seven patients who, after having presented a venous reaction, bled little. All seven of them revealed a concomitant drop in arterial pressure amounting to between three and six points.

Let us finally note that the patients, who revealed a "triple reaction" and where, for one reason or another, intervention began only 3/4 of an hour or perhaps even one hour after induction, one did not observe any abnormal hemorrhage. The vasodilating effect of histamine undoubtedly had run out in the meantime. The time interval as a matter of fact was bonded to the duration of skin manifestation which we were able to observe in other cases of massive histamine release (7). We thus believe that we can say that the abnormal bleeding, which we observed in 100 of our operated patients, was the consequence of the vasoplegic action of histamine released as a result of pethidine injection.

Let us now explain this in greater detail. Starting with the known theoretical facts and our own discoveries, we believe that the differences observed in peroperative bleeding from one patient to the next--under identical surgical, anesthetic, and hemobiological conditions--can be related to two essential phenomena, both of which are vascular in essence: one of them is the state of vasomotricity in which the small arterial and capillary vessels happen to be, while the other one involves arterial pressure.

The tonus and the contraction capacity of the small cut vessels normally outclass the intravascular blood thrust. So long as the ratio between these two forces is not upset [broken], the initial time [first-time] hemostasis, the one of arteriolar contraction, takes place normally and the hemorrhage remains feeble (this is the case in hypertension patients who do not bleed; this is also true of local anesthetics with adrenaline). But if the arterial pressure is high and if, moreover, the peripheral vessel does not contract, in other words, if it remains wide open, then the blood continues to flow and we are dealing with a case of abnormal bleeding. Hence, the subsequent times of hemostasis (plate and plasmatic times) can no longer be triggered normally and the patient on the operating table continues to bleed. This is observed every time there is a local decline in the contraction powers of the vessels (cicatricial tissues, infected tissues, tissues under histamine influence or in a state of vasodilatation). In short, the bleeding will be voluminous and can even be a cause for worry if the arterial tension remains high in regard to vessels deprived of vasomotricity and tonicity. When the arterial pressure drop is only partial, one could observe a diffuse hemorrhage, provided however that the pressure remains strong enough to force capillary and arteriolar passage. Thus we believe that we can explain this phenomenon, which is observed in certain controlled hypotension cases where the patient on the operating table bleeds in spite of a tension drop. The arteriole, deprived of all contractile



power, continues to be supplied with blood through sufficient tension. The arterial hemorrhage then recalls the venous hemorrhage; there is nothing to oppose the flow of blood except spontaneous collapse and compression performed by the surrounding tissues.

If, finally, the arterial tension drop is considerable, a new balance is established and the hemorrhage remains at a minimum. In effect, spontaneous collapse and the pressure of the surrounding tissues suffice to assure hemostasis. This is the explanation which we found for the absence of bleeding in our seven operating cases with major tension drop.

Histamine, as we know, governs the circulation of tissues to a good extent but on the other hand we do not know most of the causes capable of releasing it into the organism and very often we also do not know anything about the histamine-releasing, perhaps masked action of quite a few drugs currently used in anesthesiology, such as thiopental (11) and the natural curares (8).

In spite of these interpretation attempts, there are quite a few points which remain imprecise. Our ignorance is likewise great on the hemodynamic phenomena of the organism. This is rather poorly known and poorly explored terrain involving the momentary hemodynamic state of the operating field with respect to the hemodynamic state of these other territories of the organism. How can one explain the distribution of different circulation in two organs? We know very well that the vascular tonus and the circulatory flow rate depend, at least in part, for a given territory, on the general vascular tonus and the circulatory flow rate existing on the level of the other territories, that the arterial tension interferes in this equilibrium and that, in turn, it is influenced by the circulatory modifications which take place in the course of the intervention [operation]. But how many unknowns continue to exist in these parameters, each of which changes continually? We would like to find out more about the reasons for that.

Let us therefore say in conclusion that, when there is a venous reaction after pethidine injection, everything happens as if we were dealing with a histamine reaction. The cutaneous and subcutaneous tissues, the muscle tissues likewise, most often, lose their vasoconstriction power and we find ourselves facing a hemorrhagic operating field. Knowing that this histamine reaction is possible and that it is also the cause of bleeding is a first notion which perhaps will enable us to learn how to combat these diffuse hemorrhages which are very irritating to the surgeon.

#### Summary

→ The i.v. injection of pethidine can bring about allergic phenomena due to the endogenous release of histamine. The histamine thus released brings about vasomotor paralysis of the vessels in the muscular and skin territories and, because of that, perhaps in the beginning abnormal bleeding, provided system tension remains stable. On the other hand, if there is a concomitant tension drop, the bleeding remains within normal limits. ↗

(Study prepared by the Surgical Division, Assistant Professor E. Forster, and the Traumatology and Orthopedics Division, Dr L. Mole, L. Pasteur Hospital Center, Colmar.)

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## DISCUSSION

### Professor Vourc'h

I believe that there is no doubt that pethidine is capable of causing local phenomena at injection points. This subject was thoroughly studied in Great Britain by Dinick and Argent who devoted an article to this subject; they showed that pethidine by itself is perfectly capable of causing phenomena of local venous thrombosis, phenomena which moreover are well known to all those who use them. It remains to be determined whether these local irritation phenomena--which, I think, can, as Forster has just said, be tied to a release of histamine--are a general thing. I think that it would be very useful if one were, under these conditions, to conduct experiments on the plethysmography of the members [limbs]. If, in effect, pethidine injection into one arm is followed by marked vasodilatation in the other one, then I believe that one could prove that histamine release, a vasodilatation factor, is indeed responsible for bleeding of capillary origin. This should be perfectly possible even in the operating room and, I think, could tell us much about the hemorrhage phenomena noted by Forster and Schnoebelen. The measurement of the secretion of stomach juice, augmented by histamine, would then also be interesting.

### Dr. Schnoebelen

Finer and Partington in 1953 (Brit. Med. J., 1, 431) were able to demonstrate that the triple skin reaction, appearing after i.v. injection of pethidine is the expression of a histamine release from the tissues surrounding the perfused vein. As a matter of fact, this skin reaction is modified or diminished by the prior administration of antihistamines. They also studied the hypotensive effect of pethidine, administered i.v. in the cat and they concluded that severe hypotensions and the collapse observed in man after i.v. injection of pethidine could be related only to the release of histamine by itself.

### Professor Lareng

The problem we face here is to find out whether these phenomena are observed with pethidine only or with other medications likewise. One often injects pethidine with chlorpromazine or other drugs. Do you have similar experience with other products?

### Professor Vourc'h

Could morphine, for example, cause the same reaction?

### Dr. Schnoebelen

It is not our habit to use morphine i.v. in the course of intervention [operation]. Feldberg and Paton in 1951 (J. Physiology 114, 490) found that



the depressive action performed by morphine was concomitant with the appearance of histamine in the plasma, nevertheless, in quantities insufficient to explain, by themselves, the effect on the arterial tension.

Member of Audience

Thiopental causes a major vasodilatation. During surgery for strabismus in infants [children], for example, after the injection of thiopental, the conjunctivae become extremely red and bleeding often is more voluminous than in the case of anesthesia with halothane.

Dr. Schnoebelen

In the course of this series of observations, we were able to observe about ten skin reactions to thiopental expressed by intense rashes, located almost exclusively on the thorax. In these cases we also found, during the opening of the thorax, a particularly important hemorrhagic tendency which is even more pronounced than after pethidine reaction. On the other hand, the hemorrhage remained normal when the skin reaction to thiopental was concomitant with a major drop in the arterial pressure.

Professor Forster

In concluding I would like to say a couple of words: the purpose of our communication was to show that, when pethidine injection released histamine, the hemorrhage was at the same time abnormally severe. Vourc'h recalled that the release of histamine due to pethidine was something that had been known for 13 years; we agree, but in our opinion that is not the root of the problem. What we did want to show is that, if certain patients bleed abnormally, this may be due to the intermediary action of histamine release. Histamine release existed in cases which we presented and that much is certain; it was proved by the appearance of a typical triple reaction. Going so far as to say that abnormal and unexplained bleeding in a patient operated on is always due to histamine release seems to us to be going too far and too fast, although this is the basis of our thinking. We know rather little about abnormal hemorrhage. We must therefore go back into the entire problem of bleeding, keeping in mind the idea of histamine release; it matters little whether this is due to thiopental or pethidine or some other thing; the essential thing to us seems to be the startup of histamine movement. It is possible and even probable that histamine release is behind abnormal and unexplained bleeding. Everything would have to be reviewed and studied again from this viewpoint.

This is what I wanted to say in conclusion.